228 (1991); Kato et al., *Biochem. Biophys. Res. Comm.* **189**, 119-127 (1992); Kato et al., *J. Virol.* **67**, 3923-3930 (1993); Kurosaki et al., *Hepatology* **18**, 1293-1299 (1993); Lesniewski et al., *J. Med. Virol.* **40**, 150-156 (1993); Ogata et al., *Proc. Natl. Acad. Sci. USA* **88**, 3392-3396 (1991); Weiner et al., *Virology* **180**, 842-848 (1991); Weiner et al., *Proc. Natl. Acad. Sci. USA* **89**, 3468-3472 (1992)], and the lack of protective immunity elicited after HCV infection [Farci et al., *Science* **258**, 135-140 (1992); Prince et al., *J. Infect Dis.* **165**, 438-443 (1993)] present major challenges towards these goals.—

In The Claims:

Please amend the claims as indicated:

Cancel claims 10, 11, 18-24, 41-44 and 63-68.

1. (Four times amended) A polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, or is capable of being transcribed into a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, wherein the HCV sequence comprises, from 5′ to 3′ on the positive-sense nucleic acid, a functional 5′ non-translated region (5' NTR); one or more protein coding regions, including at least one polyprotein coding region that is capable of replicating HCV RNA; and a functional HCV 3′ non-translated region (3' NTR), wherein said polynucleotide further comprises an adaptive mutation <u>in the NS5A coding region</u> that confers improved cell culture characteristics to said polynucleotide.

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~~16~~ 86. (New) The polynucleotide of claim 1, further comprising a mutation in the NS3 or NS4B coding region.